L Number	Hits	Search Text	DB	Time stamp
1	18	polg	USPAT; US-PGPUB; EPO	2003/06/18 13:54
2	0	polg same infertil$	USPAT; US-PGPUB; EPO	2003/06/18 13:54
3	875	DNA same polymerase same gamma	USPAT; US-PGPUB; EPO	2003/06/18 13:55
4	35	DNA adj polymerase adj gamma	USPAT; US-PGPUB; EPO	2003/06/18 13:56
5	0	(DNA adj polymerase adj gamma) same male	USPAT; US-PGPUB; EPO	2003/06/18 13:55
6	0	(DNA adj polymerase adj gamma) same fertil$	USPAT; US-PGPUB; EPO	2003/06/18 13:55
7	0	(DNA adj polymerase adj gamma) same infertil$	USPAT; US-PGPUB; EPO	2003/06/18 13:55
9	3	((DNA adj polymerase adj gamma) or polg) same mutat$	USPAT; US-PGPUB; EPO	2003/06/18 13:56
10	0	((DNA adj polymerase adj gamma) or polg) same diagnos$	USPAT; US-PGPUB; EPO	2003/06/18 13:57
8	51	(DNA adj polymerase adj gamma) or polg	USPAT; US-PGPUB; EPO	2003/06/18 13:59
11	875	infertil$ near5 male$	USPAT; US-PGPUB; EPO	2003/06/18 13:59
12	1354	infertil$ same male$	USPAT; US-PGPUB; EPO	2003/06/18 14:00
13	290	infertil$ same male$ same diag$	USPAT; US-PGPUB; EPO	2003/06/18 14:00
14	0	infertil$ same male$ same diag$ same microsat$	USPAT; US-PGPUB; EPO	2003/06/18 14:01
15	3	polg adj gene	USPAT; US-PGPUB; EPO	2003/06/18 14:02
16	150748	male infertility	USPAT; US-PGPUB; EPO	2003/06/18 14:02
17	568	male adj infertility	USPAT; US-PGPUB; EPO	2003/06/18 14:02
18	1257	(male adj fertility)	USPAT; US-PGPUB; EPO	2003/06/18 14:14
19	0	((male adj fertility)) same (polg)	USPAT; US-PGPUB; EPO	2003/06/18 14:14
20	7	((male adj fertility)) same (polymerase$)	USPAT; US-PGPUB; EPO	2003/06/18 14:14

FILE 'MEDLINE, BIOSIS, CAPLUS' ENTERED AT 13:47:23 ON 18 JUN 2003

L1	44	S POLG
L2	23	DUP REM L1 (21 DUPLICATES REMOVED)
L3	1131	S DNA (1A) POLYMERASE (1A) GAMMA
L4	1153	S L3 OR L1
L5	4	S INFERT? (8A) L4
L6	2	DUP REM L5 (2 DUPLICATES REMOVED)

OMIM Home | Search | Comments

*174763 POLYMERASE, DNA, GAMMA; POLG

Alternative titles; symbols

POLYMERASE, DNA, GAMMA-1; POLG1
POLG, CATALYTIC SUBUNIT
POLG-ALPHA; POLGA

TABLE OF CONTENTS

Database Links

MEDLINE | Protein | DNA | LocusLink | Gene Map | GDB | Nomenclature

Gene Map Locus: 15q25

Note: pressing the symbol will find the citations in MEDLINE whose text most closely matches the text of the preceding OMIM paragraph, using the Entrez MEDLINE neighboring function.

TEXT

CLONING

Lestienne (1987) provided evidence for a role of DNA polymerase gamma (POLG) in the replication of human mitochondrial DNA. Bertazzoni et al. (1977) showed that the enzyme was present in both the nucleus and the mitochondria. Mitochondrial POLG is a homotetramer; see POLG2 (604983).

Based on the sequences of the S. cerevisiae and S. pombe Polg genes, Ropp and Copeland (1996) cloned the human and Drosophila POLG genes and a partial chicken Polg cDNA. The human POLG cDNA, isolated from a HeLa cell cDNA library, encodes a predicted 1,239-amino acid protein that is 78% identical to chicken Polg in the polymerase domain. Antibodies against the polymerase domain of human POLG detected a 140-kD mitochondrial protein on Western blots and immunoprecipitated a protein with POLG-like activity from mitochondrial extracts. The authors found a potentially unstable CAG repeat in the first exon of the human POLG gene.

Zullo et al. (1997) identified cloned cDNA and genomic sequences as human mitochondrial POLG

by homology with the catalytic subunit of yeast mitochondrial DNA polymerase. Lecrenier et al. (1997) cloned a human POLG cDNA by searching for ESTs with homology to yeast Polg (Mip1p). The human and yeast POLG proteins are 43% identical. Human POLG is expressed as a 4.5- to 5.0-kb mRNA that is most abundant in skeletal muscle and heart.

MAPPING

By FISH, Zullo et al. (1997) mapped the POLG gene to 15q24-q26 and the mouse Polg gene to chromosome 7. Walker et al. (1997) mapped the POLG gene to 15q25 by FISH.

MOLECULAR GENETICS

Van Goethem et al. (2001) identified a missense mutation (tyr955 to cys; 174763.0001) in the polymerase motif B of the POLG gene in a family segregating autosomal dominant progressive external ophthalmoplegia (PEO; 157640). A tyrosine at position 955 is highly conserved in DNA polymerases of different species, including the orthologous enzymes in yeast and Drosophila. In 2 families with evidence of autosomal recessive PEO, Van Goethem et al. (2001) found compound heterozygosity for 2 different missense mutations (174763.0002-174763.0004) in POLG.

Rovio et al. (1999) demonstrated that the common POLG allele is found in different ethnic groups at a uniformly high frequency (0.88) and is absent in only approximately 1% of individuals. This suggested that the common allele may be maintained by selection. Rovio et al. (2001) genotyped infertile and control males for POLG CAG-repeat lengths. Using sperm DNA from persons in whom azoospermia was excluded, they found 9 of 99 infertile males (9%) from Finland or England to be homozygous for the absence of the common allele. In contrast, the common allele was present in sperm DNA from all 98 fertile males studied, as well as in all but 6 of 522 healthy controls whose blood DNA was analyzed in parallel. Based on standard Hardy-Weinberg predictions, the 'homozygous mutant' genotype (absence of the common allele, whether or not this reflected homozygosity for a particular mutant allele) should be found in approximately 1.7% of individuals. They found the genotype at a frequency slightly below expectation in the general population, although this deviation was not statistically significant. In contrast, their finding that the 'homozygous mutant' genotype occurred in 9 of 99 infertile but 0 of 98 fertile males was highly significant. They also found a higher frequency of heterozygosity in infertile males (35%) than in fertile males (18%) or in the general population (23%). Some infertile males may be compound heterozygotes, with a second mutation elsewhere in the gene. Infertile males homozygous for the POLG mutant genotype were below the commonly accepted thresholds for at least 2 out of 3 sperm quality parameters. The POLG genotype in blood and sperm was similar in these individuals, thus excluding any effect of de novo tissue-specific mutation. Polyglutamine tracts are commonly regarded as interfaces for protein-protein interactions; thus, a sperm-specific protein could interact with this region of POLG. Given the many rounds of cell division during spermatogenesis and the functional necessity of mtDNA for sperm function, it seems plausible that a suboptimal mtDNA polymerase could result in the accumulation of mtDNA mutations and in failure to complete differentiation.

ALLELIC VARIANTS
(selected examples)

.0001 PROGRESSIVE EXTERNAL OPHTHALMOPLEGIA WITH MITOCHONDRIAL DNA DELETIONS, AUTOSOMAL DOMINANT [POLG, TYR955CYS]

In a 3-generation pedigree with autosomal dominant PEO (157640), Van Goethem et al. (2001) identified an A-to-G transition at nucleotide 2864, resulting in a tyr955-to-cys (Y955C) substitution. The tyrosine at codon 955 is highly conserved. Segregation analysis showed complete cosegregation of Y955C with autosomal dominant PEO (maximum lod = 4.01 at theta = 0.0). The mutation was present in the 8 patients and 2 of 15 at-risk individuals. It was absent in 432 control chromosomes.

.0002 PROGRESSIVE EXTERNAL OPHTHALMOPLEGIA WITH MITOCHONDRIAL DNA DELETIONS, AUTOSOMAL RECESSIVE [POLG, ALA467THR]

In a family with 3 affected sibs with presumably autosomal recessive PEO (157640), Van Goethem et al. (2001) identified compound heterozygosity for 2 missense mutations. The first was a G-to-A transition at nucleotide 1399, resulting in an ala467-to-thr (A467T) substitution. The second was a T-to-G transversion at nucleotide 911, resulting in a leu304-to-arg substitution (L304R; 174763.0003). In 2 affected individuals in another family, Van Goethem et al. (2001) identified the A467T mutation in compound heterozygous state with a different mutation, a G-to-C transversion at nucleotide 8, resulting in an arg3-to-pro substitution (R3P; 174763.0004). Three of 229 control individuals were heterozygous for A467T (allele T frequency of 0.6%). The R3P mutation was not observed in any of the control individuals.

.0003 PROGRESSIVE EXTERNAL OPHTHALMOPLEGIA WITH MITOCHONDRIAL DNA DELETIONS, AUTOSOMAL RECESSIVE [POLG, LEU304ARG]

See 174763.0002 and Van Goethem et al. (2001).

.0004 PROGRESSIVE EXTERNAL OPHTHALMOPLEGIA WITH MITOCHONDRIAL DNA DELETIONS, AUTOSOMAL RECESSIVE [POLG, ARG3PRO]

See 174763.0002 and Van Goethem et al. (2001).

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CREATION DATE

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supermim : 3/16/1992
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carol : 1/3/1991

ALLELIC VARIANTS
(selected examples)

- 0001 : PROGRESSIVE EXTERNAL OPHTHALMOPLEGIA WITH MITOCHONDRIAL DNA DELETIONS, AUTOSOMAL DOMINANT
  - Mutation : POLG, TYR955CYS
- 0002 : PROGRESSIVE EXTERNAL OPHTHALMOPLEGIA WITH MITOCHONDRIAL DNA DELETIONS, AUTOSOMAL RECESSIVE
  - Mutation : POLG, ALA467THR
- 0003 : PROGRESSIVE EXTERNAL OPHTHALMOPLEGIA WITH MITOCHONDRIAL DNA DELETIONS, AUTOSOMAL RECESSIVE
  - Mutation : POLG, LEU304ARG
- 0004 : PROGRESSIVE EXTERNAL OPHTHALMOPLEGIA WITH MITOCHONDRIAL DNA DELETIONS, AUTOSOMAL RECESSIVE
  - Mutation : POLG, ARG3PRO